Why Are Patients With Chronic Obstructive Pulmonary Disease at Increased Risk of Cardiovascular Diseases?

The Potential Role of Systemic Inflammation in Chronic Obstructive Pulmonary Disease

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Background—Chronic obstructive pulmonary disease (COPD) increases the risk of cardiovascular disease 2- to 3- fold. The factors responsible for this association remain largely unknown.

Methods and Results—We analyzed data from participants, ≥50 years of age, of the Third National Health and Nutrition Examination Survey (n=6629) to determine whether C-reactive protein (CRP) and other systemic inflammatory markers are present in participants with chronic airflow obstruction and are associated with cardiac injury. Participants with severe airflow obstruction had circulating leukocyte, platelet, and fibrinogen levels that were 460/μL (95% confidence interval [CI], 30 to 890/μL), 39 510/μL (95% CI, 21 730 to 57 290/μL), and 41.63 mg/dL (95% CI, 19.87 to 63.39 mg/dL) higher, respectively, than in those without airflow obstruction. They were also 2.18 times (95% CI, 1.46 to 3.27) more likely to have an elevated circulating CRP level. Moderate airflow obstruction was associated with smaller but still significant increases in these levels. Moderate and severe airflow obstruction was associated with increased occurrence of ischemic changes on electrocardiograms of participants. In the presence of both highly elevated CRP and moderate or severe airflow obstruction, the Cardiac Infarction Injury Score was 2.68 and 5.88 U higher, respectively, than in those without airflow obstruction and with low CRP, which suggests an additive effect of CRP and COPD on the risk of cardiac injury.

Conclusion—Low-grade systemic inflammation was present in participants with moderate to severe airflow obstruction and was associated with increased risk of cardiac injury. This may in part explain the high rates of cardiovascular complications in COPD. **(*Circulation*. 2003;107:1514-1519.)**

Key Words: chronic obstructive pulmonary disease ■ inflammation, systemic ■ C-reactive protein ■ epidemiology

Chronic obstructive pulmonary disease (COPD) is an important risk factor for atherosclerosis.[1–3] Even modest reductions in expiratory flow volumes elevate the risk of ischemic heart diseases, strokes, and sudden cardiac deaths 2- to 3-fold, independent of other risk factors.[1–5] Indeed, poor lung function has been shown to be a better predictor of all-cause and cardiac-specific mortality than established risk factors such as serum cholesterol.[3] Cardiovascular conditions are the leading cause of mortality among those with impaired lung function.[1,3,5] The mechanism or mechanisms responsible for this association, however, remain largely unknown.

Although the pathogenesis of atherothrombosis is complex and multifactorial, persistent low-grade systemic inflammation is believed to be one of the centerpieces in effecting clot formation.[6] Compelling epidemiological data link systemic inflammation to atherosclerosis, ischemic heart disease, strokes, and coronary deaths.[7,8] These observations have been strongly supported by biomedical experiments that show the direct effects of certain inflammatory markers, such as C-reactive protein (CRP), on the pathogenesis of plaque formation.[9,10]

We used population-based data from the Third National Health and Nutrition Examination Survey (NHANES III) to determine (1) whether COPD is associated with increased circulating levels of CRP and other inflammatory markers; (2) whether the intensity of the systemic inflammation is associated with the severity of airflow obstruction; and (3) whether systemic inflammation and COPD are associated with cardiac injury.

Methods

Participants

The detailed methods for NHANES III have been described previously.[11] Briefly, NHANES III was a cross-sectional, multistage probability sample conducted between 1988 and1994 that was representative of the total noninstitutionalized civilian population of

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TABLE 1. Baseline Characteristics of Participants Who Did or Did Not Have Airflow Obstruction on Baseline Spirometry

	Airflow Obstruction			
	None (n=4559)	Mild (n=1044)	Moderate (n=796)	Severe (n=230)
Demographics				
Age, y	63.2±0.3	68.1±0.5*	66.0±0.4*	66.4±0.7*
Male sex, %	40.8	58.3	52.1	50.4*
Married, %	67.5	67.9	65.4	58.5
Black, %	9.2	6.5*	7.7	5.4*
White, %	87.5	92.1*	89.8	91.3
Current smokers, %	14.4	21.9	38.4	42.4*
Lifetime nonsmokers, %	52.2	31.1	20.6	15.7
History of smoking, pack-years†	27.4±1.1	35.5±1.1*	43.4±1.1*	51.4±1.1*
BMI, kg/m^2	27.9±0.2	26.0±0.2*	26.8±0.3*	25.4±0.4*
Comorbidities				
Diabetes mellitus, %	18.5	13.0*	21.8	20.6
Congestive heart failure, %	4.9	3.8	5.9	8.8
Rheumatoid arthritis and other inflammatory conditions, %	3.0	5.2*	3.7	3.5
Symptoms, diagnosis, and medications				
Emphysema or chronic bronchitis, %	16.7	22.1*	38.4*	73.7*
Daily cough and sputum production for ≥1 y, %	3.6	7.1*	12.4*	27.7*
Bronchodilators, %	1.8	2.3	9.1*	38.8*
Inhaled or intranasal inhaled corticosteroids, %	1.0	0.5	2.2	9.4*
Oral corticosteroids, %	1.4	1.1	3.2	6.4*
Lipid-lowering drugs, %	5.5	6.8	4.6	4.9
Nonsteroidal antiinflammatories, %	11.3	8.3*	9.4	12.4
Estrogen or progesterone products, %	10.2	6.3*	6.5*	8.0
Cardiac glycoside use, %	5.0	6.1	8.4	12.2*
Physical and biochemical measurements				
Systolic blood pressure, mm Hg	136.2±0.6	138.5±0.9*	138.2±1.0	141.2±1.8*
Diastolic blood pressure, mm Hg	78.3±0.3	76.8±0.5*	76.3±0.7*	77.2±0.9
CRP levels >0.21 mg/dL, %	36.2	29.8*	45.1*	49.9*

Continuous variables are shown as mean±SEM.
*P<0.05 compared with the control (no airflow obstruction) group.
†Among current or ex-smokers.

the United States.[11] The present analysis was restricted to participants ≥50 years of age who performed spirometry that met acceptability and reliability criteria of the American Thoracic Society (n=6629).[12] We chose this age cutoff in order to improve the diagnostic accuracy of using airflow obstruction as a marker of COPD.[13]

Spirometry and Electrocardiography

Spirometry was performed with equipment that met the American Thoracic Society performance criteria.[12] To adjust for height, age, sex, and race, we used published prediction equations for forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC).[14] We used a FEV_1–FVC ratio of <0.70 to define airflow obstruction.[13] Mild, moderate, and severe airflow obstruction were defined as FEV_1 of >80% of predicted (equivalent to Stage 1 of the National Heart, Lung, and Blood Institute/World Health Organization Global initiative for chronic Obstructive Lung Disease [GOLD] classification),[13] 50% to 80% of predicted (Stage 2a),[13] and <50% of predicted (Stages 2b and 3),[13] respectively.

The NHANES cohort received a resting 12-lead ECG with a Marquette MAC 12 U.[15] An ECG coding scheme was then applied to the data to calculate a Cardiac Infarction Injury Score (CIIS) for each participant.[16] We used these scores to estimate the participants' risk of underlying ischemic heart disease. A CIIS of ≥15.0 denoted "possible or probable infarction."[17] NOVACODE ECG classification procedures were used to estimate left ventricular mass index of study participants.[17] Left ventricular mass indexes of >150 g/m^2 for men and >120 g/m^2 for women were used as cutoff points to define left ventricular hypertrophy.[15]

Laboratory Measurements

The CRP level was measured by using latex-enhanced nephelometry.[18] Because most participants had CRP values below the lowest detectable level (0.22 mg/dL), for analytic purposes, CRP was treated as a categorical rather than a continuous variable. CRP levels ≥0.22 mg/dL were considered "elevated," whereas levels >1.00 mg/dL were categorized as "highly elevated."[19] We determined serum fibrinogen; leukocyte and platelet counts; and levels of total serum cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglyceride, and apolipoproteins AI and B.[18]

TABLE 2. Serum Biochemistry Profile of Participants Who Did and Did Not Have Airflow Obstruction

	Airflow Obstruction				
	None	Mild	Moderate	Severe	P†
Circulating serum inflammatory mediators					
Leukocytes, $\times 10^3/\mu L$	7.0±0.1	7.3±0.1	7.9±0.2*	8.0±0.2*	0.001
Lymphocytes, $\times 10^3/\mu L$	2.4±0.1	2.7±0.3	3.0±0.4	2.4±0.2	0.323
Neutrophils, $\times 10^3/\mu L$	4.4±0.1	4.5±0.2	5.2±0.2	5.8±0.3*	0.115
Platelets, $\times 10^3/\mu L$	265.0±1.8	266.6±3.0	264.9±3.9	301.5±8.2*	0.001
Fibrinogen, mg/dL	308.2±3.5	311.1±6.2	334.7±5.7*	356.9±9.4*	0.001
CRP,‡ mg/dL	0.71±1.03	0.73±1.06	0.75±1.05*	1.00±1.11*	0.001
Serum lipid profile					
Total cholesterol, mg/dL	225.3±1.1	220.2±1.7	219.5±2.3	217.2±3.4	0.243
HDL, mg/dL	51.2±0.5	51.3±0.9	50.3±0.9	55.0±1.7	0.146
LDL, mg/dL	140.7±1.3	139.1±2.4	139.9±2.5	129.8±4.3	0.163
Triglycerides, mg/dL	172.6±3.2	152.7±3.5	169.4±6.0	141.7±6.4*	0.002
HDL–LDL ratio, %	40.4±0.7	41.4±1.6	40.4±1.9	46.0±3.5	0.265
Apolipoprotein Al, mg/dL	149.0±1.2	147.8±2.0	142.7±1.5	153.3±3.5	0.025
Apolipoprotein B, mg/dL	117.5±1.0	116.7±1.6	115.5±1.9	108.9±2.4	0.079

All *P* values have been adjusted for age, sex, BMI, smoking status (including pack-years of smoking), race, and various comorbidities.

*$P<0.05$ compared with the control (no airflow obstruction) group.

†All *P* values reflect a linear trend in row values from none to severe airflow obstruction categories.

‡Geometric mean.

Covariates

We classified age (in years) into 4 strata: 50 to 59, 60 to 69, 70 to 79, and ≥80. Race was divided into 3 categories: white, black, and other. Smoking status was divided into 3 strata: current, former, and never smokers. For current and former smokers, we estimated total cigarette consumption by using pack-year equivalents. We divided body mass index (BMI; in kg/m^2) into quartiles: ≤23.7, 23.8 to 26.6, 26.7 to 30.1, and ≥30.2. Presence of comorbidities was determined by participants' responses to the question: "Has the doctor ever told you had diabetes (congestive heart failure, chronic bronchitis, etc)?" Participants were deemed to have rheumatoid arthritis or a related inflammatory disorder if they had a significantly elevated titer of rheumatoid factor (≥1:40) on a serum dilution latex fixation test.[20]

Statistical Analyses

The baseline characteristics of the study participants with mild, moderate, or severe airflow obstruction were compared with controls (ie, those without any airflow obstruction) with a χ^2 test for binary variables and a *t* test for continuous variables. To assess whether there was a gradient in various baseline demographic and clinical factors across the lung function categories, we used a Mantel-Haenszel test for trend.[21] For Tables 2 and 5, we performed a weighted multiple linear regression analysis, with one degree of freedom, as a test for trend.[22] In Table 3, we used multiple linear regression techniques to estimate the independent impact of airflow obstruction on circulating levels of leukocytes, platelets, and fibrinogen.[21] We used a multiple logistic modeling technique to determine whether airflow obstruction was associated with elevations in CRP levels (Table 4).[21] In all these models, we forced in age, sex, BMI, smoking status (including pack-years), race, and various comorbidities as covariates to adjust for their potential effects on lung function and/or systematic inflammation. All tests were 2-tailed in nature. SAS version 8.1 (Cary, NC) and SUDAAN Release 8.0 (Research Triangle Institute, Research Triangle Park, NC) were used to incorporate population weights for NHANES III. Continuous variables are shown as mean±SEM, unless otherwise indicated.

Results

There were 6629 participants in this analysis (45.0% males). The average age of the participants was 64.4±0.3 years; 2070 (31.2%) had airflow obstruction on their spirometry; and 19.0% were current smokers. The average BMI was 27.4±0.1 kg/m^2. The baseline characteristics of the study

TABLE 3. Adjusted Relationship Between Severity of Airflow Obstruction and Circulating Levels of Inflammatory Markers

	Airflow Obstruction		
	Mild	Moderate	Severe
Leukocytes, $\times 10^3/\mu L$	0.10 (−0.10, 0.30)	0.42 (0.13, 0.71)*	0.46 (0.03, 0.89)*
Platelets, $\times 10^3/\mu L$	8.03 (1.54, 14.52)*	2.34 (−3.58, 8.26)	39.51 (21.73, 57.29)*
Fibrinogen, mg/dL	0.95 (−9.03, 10.93)	18.35 (6.83, 29.87)*	41.63 (19.87, 63.39)*

Each cell contains the β-coefficient (95% CI) of each variable, adjusted for age, sex, BMI, smoking status (including pack-years of smoking), race, and various comorbidities. Reference group: participants without airflow obstruction.

*$P<0.05$ compared with the control (no airflow obstruction) group.

TABLE 4. Relative Odds of Having an Elevated Level of Circulating CRP

	Airflow Obstruction		
	Mild	Moderate	Severe
CRP ≥0.22 mg/dL	0.84 (0.63, 1.11)	1.41 (1.07, 1.87)*	2.18 (1.46, 3.27)*
CRP >1.00 mg/dL	0.99 (0.67, 1.47)	1.56 (1.06, 2.30)*	2.74 (1.59, 4.72)*

Each cell contains the relative odds (95% CI) of each variable, adjusted for comorbidities, BMI, smoking status, age, race, and sex. Reference group: participants without airflow obstruction.

*$P<0.05$ compared with the control (no airflow obstruction) group.

population stratified according to the severity of airflow obstruction are shown in Table 1. Male sex and current smoking status were positive risk factors for severe airflow obstruction, whereas BMI was inversely correlated with lung function. Systolic blood pressure was elevated in those with severe airflow obstruction compared with controls. After adjustments for confounding factors, systolic blood pressure was on average 4.0 mm Hg (95% confidence interval [CI], 0.4 to 7.6) higher among participants with severe airflow obstruction than among the controls. There were no significant differences in systolic blood pressure between the other lung function groups ($P=0.948$ for mild; $P=0.790$ for moderate groups). Compared with the controls, diastolic blood pressure was 1.4 mm Hg (95% CI, 0.1 to 2.6) lower among participants with moderate airflow obstruction ($P=0.034$) but was similar among participants with mild or severe airflow obstruction ($P=0.545$ for mild; $P=0.653$ for severe).

The circulating levels of leukocytes, platelets, fibrinogen, and CRP were higher in participants with than in those without airflow obstruction. The highest levels for all of these inflammatory markers were observed in the group with severe airflow obstruction (Table 2). Adjustments for confounders made little difference to the overall results (Tables 3 and 4). We observed that participants with severe airflow obstruction had leukocyte, platelet, and fibrinogen levels that were on average 460/μL, 39 510/μL, and 41.63 mg/dL higher, respectively, than those of the controls. In an analysis that excluded those on oral corticosteroids, we found that leukocyte, platelet, and fibrinogen levels were on average 400/μL, 37 590/μL, and 40.39 mg/dL higher, respectively, than those of the controls. The increases in leukocyte count among those with severe airflow obstruction were driven largely by the neutrophilic subpopulation of cells (Table 2). Participants with severe airflow obstruction were also 2.18 and 2.74 times more likely to have elevated and highly elevated circulating CRP levels than the controls (Table 4). Participants with moderate airflow obstruction had smaller increases in circulating leukocyte, fibrinogen, and CRP levels. Mild airflow obstruction was not associated with elevations in any of these measurements.

Lipid profiles among the 4 groups are shown in Table 2. There were no significant differences in the LDL, apolipoprotein B, or HDL concentrations among the groups. Participants with severe airflow obstruction had slightly lower serum concentrations of triglycerides and a slightly raised apolipoprotein AI levels.

There were important differences in ECG findings among the 4 lung function groups (Table 5). Compared with the control group, mild, moderate, and severe airflow obstruction were associated with an increase in CIIS of 0.38±0.48 ($P=0.437$), 2.38±0.53 ($P=0.001$), and 3.62±0.76 ($P=0.001$) U, respectively. Compared with controls, those with severe airflow obstruction were 2.1 times more likely to have ECG evidence of probable or possible (prior) myocardial infarction (adjusted odds ratio [OR] 2.12; 95% CI, 1.37 to 3.29). This risk was also elevated among those with moderate airflow obstruction (adjusted OR, 1.38; 95% CI, 1.04 to 1.82) but not in those with mild airflow obstruction (adjusted OR, 1.28; 95% CI, 0.95 to 1.72).

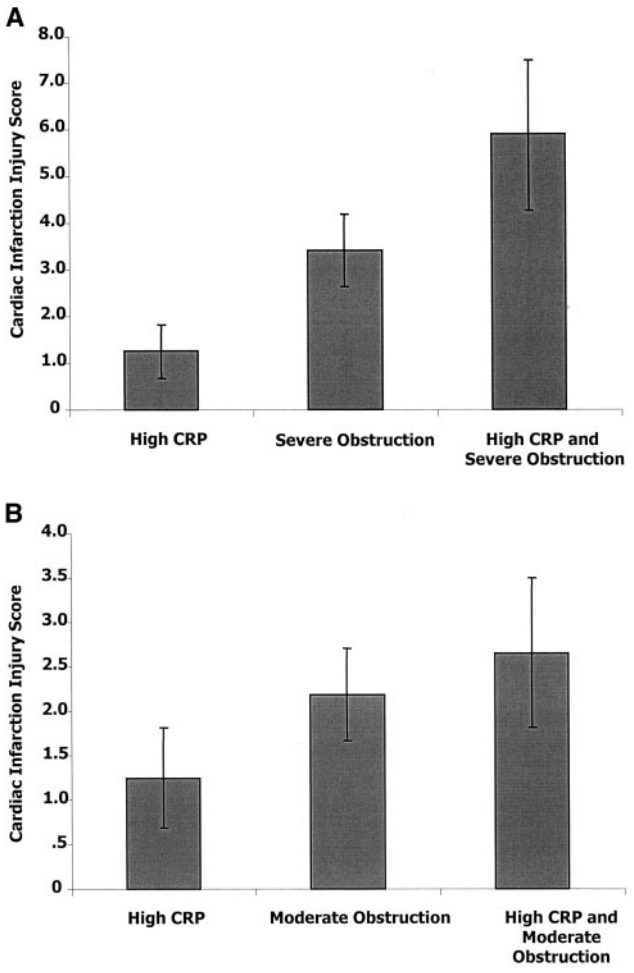
Because CIIS may be confounded by a variety of factors, including presence of pulmonary hypertension and digitalis use, we performed a series of subgroup analyses that excluded participants with these characteristics. First, we excluded participants with ECG evidence of right ventricular hypertrophy (defined as R amplitude greater than S amplitude

TABLE 5. Summary of Electrocardiographic Findings Among Participants With and Without Airflow Obstruction

	Airflow Obstruction				
	None	Mild	Moderate	Severe	*P* for Trend†
Sinus rhythm, %	86.4	83.5	83.1	78.1*	0.102
Probable/possible prior myocardial infarction, %	14.6	21.1	22.8*	29.7*	0.001
CIIS	6.5±0.2	7.9±0.4	10.0±0.5*	11.2±0.8*	0.001
Left ventricular mass index, g/m^2	106.6±0.6	109.4±1.1	109.9±1.8	106.3±2.2	0.098
Left ventricular hypertrophy, %	11.8	10.8	15.0	13.4	0.478
Right-axis deviation (QRS or P), %	3.6	6.1	7.8*	24.3*	0.001
Right ventricular hypertrophy, %	21.9	22.4	21.5	13.2*	0.105

*$P<0.05$ compared with the control (no airflow obstruction) group.

†*P* values reflect a linear trend in row values from none to severe airflow obstruction categories. All *P* values have been adjusted for age, sex, BMI, smoking status (including pack-years of smoking), race, and various comorbidities.



A, Relationship of CRP and severe airflow obstruction to CIIS (*P* for trend=0.001). B, Interaction of CRP and moderate airflow obstruction to CIIS (*P* for trend=0.001). The shaded bars represent increases in CIIS adjusted for a variety of factors (see Methods) relative to a group without airflow obstruction and with low CRP. High CRP is defined as >1.00 mg/dL. The error bars represent SEM.

in V_1 or V_2) or right-axis deviation (defined as QRS or P axis of >90°). In this subgroup analysis, we found that compared with controls, mild, moderate, and severe airflow obstruction were associated with an increase in CIIS of 0.81±0.59 (*P*=0.174), 2.51±0.61 (*P*=0.001), and 3.55±1.05 (*P*=0.001) U, respectively. In an analysis that excluded participants with a history of current cardiac glycoside use, mild, moderate, and severe airflow obstruction were associated with an increase in CIIS of 0.38±0.48 (*P*=0.437), 2.38±0.53 (*P*=0.001), and 3.62±0.76 (*P*=0.001) U, respectively.

There was a significant correlation between CRP and CIIS. Individuals with highly elevated CRP levels had CIIS values that were 1.25±0.56 (*P*=0.029) U higher than those with low CRP levels. We observed an additive effect of airflow obstruction and CRP on CIIS. Individuals with severe airflow obstruction and highly elevated CRP levels had CIIS that were, on average, 5.88±1.61 U higher than those of participants with no airflow obstruction and with low CRP levels (Figure, A). A similar interaction was observed for moderate airflow obstruction and highly elevated CRP (increase of 2.68±8.59 U; Figure, B).

Discussion

Using a very large amount of population-based data, we have made several relevant observations that may have important implications for future COPD management and research. First, although previous studies have shown that severe COPD patients have elevated circulating levels of tumor necrosis factor, endothelin-1, interleukin-6, and CRP compared with healthy controls,[23–26] these studies were limited by small sample sizes and restriction of study subjects largely to those with severe COPD (FEV_1 <50% of predicted). Our present study extends these findings by demonstrating the presence of systemic inflammation even in moderate COPD (FEV_1 50% to 80%). These data may explain why even relatively small reductions in FEV_1 can increase the risk of cardiovascular morbidity and mortality 2- to 3-fold in the general community.[1–5]

Second, although prior studies have shown systemic inflammation in severe COPD,[23–26] none of these studies have established a link between systemic inflammation in COPD and cardiac injury. Our findings indicate that airflow obstruction is an important risk factor for cardiac injury. In the presence of elevated CRP, the risk increases almost 2-fold, which suggests an important interplay of systemic inflammation with airflow obstruction in the development of ischemic heart disease (see Figure, A and B).

Our observations are similar to those of Cirillo et al,[27] who showed an inverse association between FEV_1 and serum CRP. Unlike our study, however, they included all adult NHANES participants (increasing the risk of confounding by age). They also did not use a prediction equation for FEV_1 to adjust for differences in age, sex, height, and race of study participants, which could have led to residual confounding by these variables.[17] More importantly, the study by Cirillo et al[27] did not evaluate the role of airflow obstruction (or its severity) on systemic inflammation. We have extended the findings of Cirillo et al[27] and have shown that moderate to severe (but not mild) COPD is strongly associated with systemic low-grade inflammation and ECG evidence of ischemic heart disease.

We have concentrated on CRP in the present study because it has been shown to upregulate the production of proinflammatory cytokines and tissue factors by monocytes, increase the uptake of LDL by macrophages, and directly induce expression of adhesion molecules by human endothelial cells.[28] Additionally, CRP may deposit directly into the arterial wall during atherogenesis, interacting with other inflammatory mediators to create foam cells, which serve as building blocks of atherosclerotic plaques.[10] Serum fibrinogen may promote atherosclerosis by increasing blood viscosity and acting as a cofactor for platelet aggregation.[29] Leucocytosis and thrombocytosisalso promote plaque formation but likely through different pathways.[29] Because neutrophilic inflammation may destabilize atherosclerotic plaques, leading to their rupture, our finding of increased circulating neutrophils among participants with severe airflow obstruction also may be relevant.[30]

Several limitations of this study should be emphasized. First, we do not know whether the reduction of proinflammatory markers would improve prognosis in COPD. Future studies are needed to determine if certain therapies that

reduce the burden of systemic inflammation can lead to improved cardiovascular outcomes in COPD. Second, there may be alternate mechanistic pathways that may be responsible for cardiovascular complications in COPD. Among our study cohort, severe airflow obstruction was associated with elevated resting systolic blood pressure. Although the differences in blood pressure were slight and not associated with increased left ventricular mass, the possibility exists that the blood pressure increases represent excess sympathetic nervous activity in severe COPD.[31] Future work is needed to determine what role (if any) the autonomic nervous system plays in the pathogenesis of adverse cardiovascular events in COPD. Third, medication effects on circulating CRP and other inflammatory markers should also be considered. Systemic corticosteroids, for instance, may decrease CRP levels[32] while slightly increasing circulating levels of leukocytes and platelets.[33] Exclusion of individuals who were taking oral corticosteroids made no difference to the overall findings, which suggests that this medication was not an important confounder in the analysis.

Over the next 20 years, nations across the world will experience a dramatic rise in COPD-related morbidity and mortality.[13] Data from the present study confer a plausible mechanism to explain the strong relationship between COPD and cardiovascular diseases. More importantly, they extend the current concept of COPD as a systemic inflammatory disorder (and not just an inflammatory disorder of the pulmonary system) and provide potential new therapeutic targets to reduce cardiovascular complication rates in COPD.

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